II. Remarks

A. Status of the Claims

Claims 1-8 and 11-20 are currently pending in this application. Claims 1-8 have been allowed. Claims 9-10 and 21-26 were previously canceled.

Prior to addressing the current rejections, Applicants wish to thank the Examiner for removing the rejection of claim 1 under 35 U.S.C. 102(b), for removing the rejection of the associated dependent claims 2-8 under 35 U.S.C. 112, second paragraph, and for indicating that claims 1-8 are allowed. Applicants also wish to thank the Examiner for removing the rejection of claims 2, 4, 6, 8, 12, 14-16, and 18-20 under 35 U.S.C. 112, second paragraph.

B. Review of the Current Rejections

The Examiner maintained the rejection of claims 17-20 under 35 U.S.C. 112, first paragraph, scope of enablement for diagnostic methods utilizing polypeptides.

The Examiner maintained the rejection of claim 11 under 35 U.S.C. 102(b) as being anticipated by Horwitz et al (U.S. Patent No. 5,108,745).

The Examiner maintained the rejection of claims 12-16 under 35 U.S.C. 112, second paragraph, as being indefinite for dependence from a rejected claim.

C. Claim Rejections - 35 U.S.C. §112, first paragraph

1. Claims 17-20

a. Methods utilizing M. tuberculosis proteins were known in the art at the time of the invention.

In the Office Action, claims 17-20 were rejected under 35 U.S.C. 112, first paragraph. The Examiner alleged that "the instant specification contains no working examples of methods for detecting *M. tuberculosis* infected hosts or hosts susceptibility to *M. tuberculosis* utilizing the listed polypeptides or any other compositions."

This rejection is respectfully traversed. Applicants submit that methods of utilizing other *M. tuberculosis* proteins were known in the art at the time of the invention. The Examiner is reminded that "if all other factors point toward enablement, then the absence of working examples will not by itself render the invention non-enabled. In other words, lack of working examples . . . should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement." MPEP 2164.02. Applicants submit that, in view of the guidance

provided by the instant specification combined with the knowledge of one of skill in the art at the time of the invention, one of skill in the art would be enabled to practice the presently claimed invention.

In support of this position, Applicants respectfully point out that the instant application teaches a strong likelihood of immunogenic properties of the claimed polypeptides. See, e.g., pp. 13-17 of the specification. The instant application further teaches a group of open reading frames encoding polypeptides that are secreted by *M. tuberculosis*. See, e.g., Figure 2 of the specification. These sequences were isolated using sophisticated methods designed to identify polypeptide sequences with a high likelihood of coding for polypeptides with immunogenic properties. The instant specification also teaches methods of using such polypeptides, or segments thereof, to diagnose whether a subject has been infected with *M. tuberculosis*. See, e.g., claims 17-20.

Applicants further submit that the state of the art at the time of the invention corroborated the strong likelihood of immunogenic properties of the claimed polypeptides and enabled testing to confirm such properties. Applicants respectfully submit that at the time of the invention, it was known in the art that "a large number of mycobacterial proteins are able to induce an immune response." Young D. B. et al., *Mycobacterial protein antigens: a compilation*, Mol. Microbiol. 6:133-145 (1995) (IDS containing this article has been filed concurrently with this response). In particular, several extracellular proteins have been shown to induce immune responses to *M. tuberculosis*. Horwitz et al. demonstrated that immunization with purified extracellular proteins of *M. tuberculosis* induced protective immunity against *M. tuberculosis* via cutaneous DTH response analysis in guinea pigs. Horwitz et al., *Protective immunity against tuberculosis induced by vaccination with major extracellular proteins of Mycobacterium tuberculosis*, Proc. Natl. Acad. Sci. USA, 92:1530-1534 (1995) (disclosed in IDS filed on November 2, 2001). Manca et al., utilizing competitive enzyme-linked immunosorbent assay (ELISA), demonstrated "that MPT63 induces immune responses during TB" and remarked that "many of the[] proteins [that are actively secreted by *M. tuberculosis* during growth] have been shown to generate protective immune responses in animal models." Manca et al., *Molecular Cloning, Purification, and Serological Characterization of MPT63, a Novel Antigen Secreted by* Mycobacterium tuberculosis, Infection and Immunity 65(1):16-23 (1997) (disclosed in IDS filed on November 2, 2001). Further, in a separate study also using ELISA, Manca et al.

demonstrated that "MTC28 elicited strong immune responses in BCG-immunized guinea pigs . . . ." Manca et al., *MTC28, a Novel 28-Kilodalton Proline-Rich Secreted Antigen Specific for the* Mycobacterium tuberculosis *Complex,* Infection and Immunity 65(12):4951-4957 (1997) (disclosed in IDS filed on November 2, 2001).

Applicants respectfully submit that in this case, the instant specification, together with what was known in the art at the time of the invention (i.e. working examples of secreted *M. tuberculosis* proteins that induce immunogenic responses), provides ample guidance to enable one skilled in the pertinent art to make and use the invention in accordance with claims 17-20 without undue experimentation.

b. <u>There is adequate foundation that the whole polypeptide induces an immune response.</u>

In making the rejection, the Examiner further alleged that "there is no foundation for the enablement of segments because there is insufficient support for methods utilizing the whole polypeptides in question." However, Applicants submit that, as admitted by the Examiner, the "determination of segments with a desired application may not be undue experimentation," but such a determination should be "based upon a foundation that the whole polypeptide functions as required." Applicants submit that the foundation of the whole polypeptide functions have been supplied by the instant specification, along with the knowledge of one of skill in the art.

As discussed above, the prior art discloses working examples of methods utilizing *M. tuberculosis* proteins to elicit an immune response. The instant specification discloses working examples of ELISA tests by which the antigenicity of proteins can be analyzed and further discloses the sequences of the polypeptides in question. Together, these items provide ample guidance to one skilled in the pertinent art to practice the claimed invention without undue experimentation. The methods employed by Applicants to isolate the sequences in question established a high likelihood that the isolated sequences would yield an immune response, i.e. "that the whole polypeptide [would] function[] as required" and therefore provides an adequate foundation for the enablement of segments of the polypeptides in question. Because there is adequate foundation for the enablement of diagnostic methods utilizing the entire polypeptide sequences, there is adequate foundation for the enablement of diagnostic methods utilizing segments of such sequences.

Accordingly, Applicants respectfully request that the rejection of claims 17-20 under 35 U.S.C. 112, first paragraph, be removed.

2. Claims 12-16

In the Office Action, claims 12-16 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for dependence from a rejected claim.

In response, Applicants respectfully submit that in light of the arguments presented in section D. below, claim 11 is in condition for allowance. As such, Applicants respectfully request that the rejection of claims 12-16 under 35 U.S.C. 112, second paragraph, be removed, as these claims will no longer depend from a rejected claim when the rejection of claim 11 under 35 U.S.C. 102(b) is removed.

D. Claim Rejections - 35 U.S.C. § 102(b)

In the Office Action, the Examiner rejected claim 11 as being anticipated by Horwitz et al. (U.S. Pat. No. 5,108,745) (hereinafter "Horwitz"). The Examiner alleged that "the proteins taught by Horwitz et al. are the *M. tuberculosis* secreted proteins," and placed the burden on Applicants "to show a novel or unobvious difference between the claimed product and the product of the prior art." Prior to addressing this rejection, Applicants wish to point out that the specification of the instant application defines MTSP as "*M. tuberculosis* secreted polypeptide" (see page 10 of the instant specification), not "*M. tuberculosis* secreted protein" as stated by the Examiner.

This rejection is respectfully traversed. Applicants respectfully submit that Horowitz et al. fails to teach or suggest an isolated polypeptide with an amino acid sequence selected from a group consisting of the sequences of six specific polypeptides set forth in claim 11.

1. The "extracellular product of *Mycobacterium tuberculosis*" and the "*Mycobacterium tuberculosis* major extracellular protein" of Horwitz are not identical to the "isolated polypeptide" of claim 11 of the instant application.

Applicants respectfully submit that the protein of Horwitz is only generally directed to extracellular proteins or major extracellular products in accordance with claims 13-17 of Horwitz. Horwitz does not disclose the amino acid sequence of such a protein. Applicants further submit that the specification of Horwitz does not disclose the "*M. tuberculosis* secreted

polypeptides" or "isolated polypeptides" of claim 11 of the present invention; the only reference to *M. tuberculosis* proteins are found in claims 13, 14, 16, and 17 of Horwitz. On the other hand, the isolated polypeptide of claim 11 of the instant application comprises a specific amino acid sequence selected from a group of six enumerated sequences.

However, claim 11 of the present specification is directed to an isolated polypeptide with an amino acid sequence selected from the group consisting of the sequences of the six polypeptides enumerated in claim 11. The instant specification defines "isolated polypeptide" as "a polypeptide which either has no naturally-occurring counterpart, or has been separated or purified from components which naturally accompany it." See page 5 of the specification. Whereas Horwitz necessarily deals with entire proteins (i.e. "major extracellular protein" and "extracellular products"), the instant application exploits the utility of specific polypeptide sequences from *M. tuberculosis* proteins (i.e. the sequences set forth in claim 11).

2. The Horwitz protein does not necessarily possess the characteristics of the isolated polypeptide of claim 11 of the instant application.

Applicants further submit that the protein described in Horowitz does "not necessarily or inherently possess the characteristics" of the isolated polypeptide covered by claim 11. *In re Best*, 562 F.2d 1252, 1255, 195 U.S.P.Q. 430 (CCPA 1977). The Examiner is reminded that "a prior art reference that discloses a genus still does not inherently disclose all species within the broad category but must be examined to see if a disclosure of the claimed species has been made or whether the prior art reference merely invites further experimentation to find the species." MPEP 2112 IV, citing *Metabolite Labs, Inc. v. Lab Corp. of Am. Holdings*, 370 F.3d 1354, 1367 (Fed. Cir. 2004) (internal quotation marks removed). In this case, Horwitz makes reference to a very broad genus because it merely recites an "extracellular product of *Mycobacterium tuberculosis*" and a "*Mycobacterium tuberculosis* major extracellular protein" in the claims with no additional guidance as to the species that would be encompassed by this broad genus. The protein of Horwitz is described far too general of terms to establish that it inherently possesses any of the specifically identified characteristics of the isolated polypeptide of claim 11.

Even assuming *arguendo* that the genus disclosed by Horwitz encompasses the polypeptide species of the instant application, Horwitz fails to disclose the claimed polypeptide species, and further, Horwitz fails to "merely invite further experimentation" to find the *M. tuberculosis* polypeptide species disclosed by the instant application or suggest the identification

of the sequences in claim 11 of the instant application. Applicants have isolated the 6 sequences of claim 11 from a pool of nearly 4,000 predicted proteins by the analysis of the *M. tuberculosis* genomic sequence. See page 14 of the specification. Thus, it is only with the benefit of hindsight bias of the present specification that one skilled in the pertinent art would be motivated to isolate the polypeptide of claim 11 upon reading the general disclosure of Horwitz.

In light of the foregoing, Applicants respectfully submit that the "extracellular product of *Mycobacterium tuberculosis*" and the "*Mycobacterium tuberculosis* major extracellular protein" of Horwitz "do not necessarily possess the characteristics of" the *M. tuberculosis* isolated polypeptides of claim 11 of the instant application. See MPEP §2112.01. Further, Applicants reiterate the prior argument that Horwitz does not teach each and every element of claim 11 of the instant application. See Applicants' previous Office Action response dated April 14, 2008, page 8. Accordingly, Applicants respectfully request that the rejection of claim 11 under 35 U.S.C. 112, first paragraph, be removed.

V. Conclusion

In view of the amendments made and arguments presented, it is believed that all claims are in condition for allowance. If the Examiner believes that issues may be resolved by a telephone interview, the Examiner is invited to telephone the undersigned at (973)422-6532. The undersigned also may be contacted via e-mail at lschroeder@lowenstein.com. All correspondence should be directed to our address listed below.

AUTHORIZATION

The Commissioner is hereby authorized to charge any fees that may be required, or credit any overpayment, to Deposit Account No. 50-1358.

Respectfully submitted,
Lowenstein Sandler PC

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